Quality of life assessment using patient reported outcome (PRO) measures - still a Cinderella outcome?

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"….the person who takes medicine must recover twice, once from the disease, and once from the medicine" William Osler (1849-1919)

William Osler was one of the first physicians to articulate the harms not just the benefits of modern medicine and a century since his pithy observation, we have seen many exciting advances made in the treatment of cancer. Better understanding of molecular biology together with improved diagnostics, surgical and radiotherapy techniques and innovative, more targeted systemic therapies mean that more patients have a genuine prospect of cure or surviving longer with their disease. Nothing comes without cost however and the iatrogenic harms and burdens, both acute and long-term, associated with novel drug therapies, remain under-reported, under-estimated and consequently under-treated.[1] To enable wise decision-making before embarking on different therapeutic management strategies, patients and doctors need much more information than that usually available in publications of many clinical treatment trials. How one functions and feels during and after treatment are salient concerns yet primary outcomes of studies are invariably overall survival (OS) and more commonly in advanced disease, progression free survival (PFS). The paper by Marandino et al. [2] shows an alarming dearth of quality of life (QoL) endpoints in major clinical trials of novel therapies in the common solid tumours. The authors illustrate how even when patient assessments were included in the trials, the results were generally insufficiently reported, subject to significant publication delays long after those of the main trial and were often found in low impact journals.

We have to do better in our evaluation of expensive novel products. The sometimes modest OS or more often PFS gains that excite clinical scientists and pharma share-holders, may be of little value to patients experiencing some serious and burdensome side-effects. Conclusions stating that 'patients found side-effects tolerable' should be viewed with some skepticism as trials that are conducted for registration and licensing purposes rarely have lengthy enough follow-up to chart some of the problems that emerge later in the clinic.[3]

There are many other reasons to be concerned about the quality of the traditional adverse event (AE) data derived from clinical trials. There is a lack of concordance between toxicity and symptom recording by patients using PROs and the 'gold-standard' for establishing AEs namely the Common Terminology Criteria of Adverse Events (CTCAEs) graded by clinicians.[4] Worryingly although AE grades are regarded as objective many even experienced clinicians are unaware of the precise definitions for the different grades. Furthermore studies show quite poor inter-rater reliability between clinicians asked to rate the same symptom. [5]

Unfortunately there is little reason for complacency about some of the trial publications that do include QoL from patient reported outcome measures (PROMs). A myriad of deficiencies can be observed including: - inappropriate choice of PRO,

inadequate descriptions as to how missing data were handled and naïve or biased statistical methods to name but a few.

Just because a questionnaire purports to measure quality of life, this does not necessarily mean that it is suitable for the patient population, their disease status or the treatments being trialed. Many commonly used generic PROMs such as the EORTC-QLQ-C30 [6] and the FACT-G [7], which are multi-dimensional with domains covering areas such as physical, functional, social, sexual and emotional well-being. Reporting merely the mean total scores from such measures can mask or dilute important effects, both positive and negative, that might exist at a domain level. Both the EORTC and FACT-G can be accompanied by disease specific modules or subscales that contain important relevant items. The FACIT system has a whole suite of subscales that are treatment specific permitting better evaluation of symptoms associated with, for example, monoclonal antibodies, TKIs, hormone therapies, taxanes and anti-angiogenisis drugs.[8]

In oncology trials especially those conducted in tumour sites with a poor prognosis or in advanced disease, attrition is inevitable and a major challenge. If one treatment arm is significantly more effective than another, then missing data are unlikely to be missing at random and sophisticated statistical methods are required. At the very least it is vital that at an individual item, questionnaire or patient level, the reasons for missing data be that toxicity, progression or death, are available for scrutiny.

CTCAE grades only offer information regarding the presence at any time of a symptom. Good PRO measures when analyzed appropriately, can provide a clearer description of the trajectory of important side effects, when they start, if they ever improve or if they persist until end of treatment. Group mean scores are not very helpful for individual decision-making, so responder analyses showing what proportion of patients, in each treatment arm, at each time point, ever improve from baseline, remain stable or decline are useful for decision-making.

There are many suitable rigorously validated PRO measures to consider if we are serious about charting the multiple, putative harms and benefits of novel drugs. Both the FDA and the EMA have recognised the need and published guidance on measures they would consider for label claims. [9, 10]

Trialists might also think about including the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) developed by the US National Cancer Institute (NCI) initiative to introduce patient-reported outcomes as a standard component of adverse-event monitoring in NCI-sponsored trials. [11]

Any endpoint in a clinical trial requires thought, and it is important to challenge the cynical viewpoint still held by some that QoL endpoints are something that has to be included but is not really that pertinent for pharmacovigilance or decision-making. The unscientific approach of adding in any vaguely relevant measure to the trial protocol as an afterthought must end. Finally if conducted well with employment of rigorous methodology, then proper respect should be given to the resultant patient reported data which deserve to be published fully along with the main study results.

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